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14. ABSTRACT: Lymphedema is a common complication of primary breast cancer therapy. It is a chronic, insidiously progressive, and potentially devastating condition. Radiation increases patients' lymphedema risk since conventional fields encompass residual functioning lymphatics. Imaging technologies may identify these lymphatics and allow the construction of radiation fields that minimize their radiation exposure while preserving loco-regional tumor control. This study uses SPECT scanning to anatomically localize lymphatics critical for arm drainage after surgical removal of axillary lymph nodes. The study will determine the feasibility of fusing SPECT images with CT scans used in radiation planning to quantify radiation dosimetry. The study tests the hypothesis that changes in arm volume will correlate with radiation doses delivered to lymphatic critical for arm drainage. The fact that higher doses of radiation and larger radiation ports are associated with an increased incidence of lymphedema (volume $\uparrow \geq 150\text{ml.}$), particularly severe lymphedema (volume $\uparrow \geq 400\text{ml.}$), supports this hypothesis. The proposed study realizes the BCRP goals by elucidating a novel means of refining breast cancer treatment to minimize patients' risk of developing the most prevalent and dreaded complication of conventional primary therapy, lymphedema.						
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Table of Contents

Cover.....	
SF 298.....	2
Table of Contents.....	3
Introduction.....	4
Body.....	5
Key Research Accomplishments.....	9
Reportable Outcomes.....	10
Conclusions.....	11
References.....	12
Appendices.....	13

Introduction:

This career development award has dual aims. As a training award, the first aim involves the recipients' completion of a Masters degree in Clinical Epidemiology with an emphasis on research methodology and biostatistics. The second is completion of a prospective cohort study to determine if the radiation dose delivered to lymphatics essential for arm drainage correlates with increased ipsilateral arm volume. Lymphedema is the number one survivorship issue in breast cancer (American Cancer Society). Affected patients experience reduced quality of life and are more likely to develop social, vocational, psychological and functional decline (Maunsell, Passik). Current imaging approaches, e.g. SPECT scanning, may permit the precise anatomic localization of lymphatics critical for arm draining following axillary surgery (Czerniecki, Joensuu, Witte). Fusion of SPECT images with the CT scans used in radiation planning offers the possibility of quantifying radiation dosimetry to lymphatics (Chao). Such quantification allows testing of the hypothesis that increased radiation exposure correlates with lymphatic congestion manifest as increased inter-limb arm volume discrepancy (Liljegren, Meek). Testing this hypothesis and establishing the feasibility of SPECT-CT fusions are requisite initial steps in the development of radiation planning techniques that deliberately excluded lymphatics critical for arm drainage and thereby reduce patients' lymphedema risk.

Body:

Prior to each section of the report, relevant text from the initial Statement of Work has been included.

Task 1. Complete course work and thesis preparation for a Masters of Science degree in clinical epidemiology and the University of Pennsylvania Center for Clinical Epidemiology and Biostatistics.

- a. Course work - Classes will be taken over the course of four semesters at the CCEB (Months 1 - 24)
- b. Thesis completion - The thesis will be written under the guidance of a senior CCEB faculty member. This will be completed during the third year of study. (Months 25 - 36)

The recipient, Dr. Cheville, was awarded the degree of Master of Clinical Epidemiology on May 15, 2006. All requisite coursework (Appendix A) and preparation of her Masters thesis (Appendix B) was completed in accordance with the timeline initially proposed in the Statement of Work.

The recipient's intention on grant submission was for the research project proposed in the grant to serve as the focus of her Masters thesis. Due to slower than anticipated subject recruitment, sufficient data would not have been collected within the three year interval proposed for completion of her Masters Degree. For this reason, an alternate thesis project was proposed to the faculty of the Center for Clinical Epidemiology and Biostatistics and accepted.

Dr. Cheville analyzed a large cross-sectional dataset collected from Stage IV breast cancer patients for the purpose of characterizing rehabilitation needs and service utilization. Important findings included: 1. Physical impairments were identified in 150 (92%) subjects, and 144 subjects (88%) required some type of rehabilitative intervention; 2. Physical impairments that required hospitalization were overwhelmingly more likely to receive rehabilitation, OR 87.88 (95% CI 28.46 - 271.36), and PT/OT, OR 558.75 (95% CI 186.99 - 1669.61); 3. Subjects' race and socioeconomic status predicted receipt of rehabilitation services. These findings have not been previously reported in a cancer cohort. The manuscript is currently undergoing revision and text reduction in preparation for submission to the Journal of the National Cancer Institute.

Task 2. Conduct a prospective cohort study to estimate the increased lymphedema risk associated with radiation therapy delivered to chest wall and lymph node beds. (Months 1-36)

- a. Subject enrollment - A total of 50 subjects will be enrolled in the study. An average of 130 TXN1M0 breast cancer patients is seen at the University of Pennsylvania Cancer Center each year. Estimating a conservative accrual rate of 3 patients per month, subject enrollment will require 17 months. (Months 1-17). Contingent on the approval of the USAMRMC HSRRB, subject enrollment may commence prior to the dispensation of the BCRP Physician Scientist Training Award.
- b. Data Collection - Once enrolled, subjects will be followed for 12 months. Data will be collected at 2 time points: **A.** baseline (prior to radiation therapy), **B.** 12 months after initiation of radiation therapy. (Months 1 - 29)
- c. Institutional Review Board approval - This protocol has been approved by the University of Pennsylvania Institutional Review Board and the University of Pennsylvania Cancer Center Clinical Trials Scientific Review and Monitoring Committee. The protocol has been submitted to the USAMRMC HSRRB and approval is pending. (Completed prior to Physician Scientist Training Award dispensation)
- d. Data entry - Data entry will occur concurrently with data collection. All data will be entered one month following the completion of data collection. (Months 1 - 30)
- e. Data analysis - Data analysis will commence following completion of data entry. It is anticipated that analysis will require two months. (Months 31 - 32)
- f. Manuscript preparation - Preparation of manuscripts will require 4 months. (Months 32 - 36).

a. Subject enrollment

Thirty subjects have been enrolled in the study over the past 14 months. Subject recruitment was delayed by the need for the approval of three regulatory bodies; the USAMRMC Review Board, the University of Pennsylvania Institutional Review Board, and the Abramson Family Cancer Institute Clinical Trials Committee. Recruitment was further delayed by the need to determine the optimal: amount of radiolabeled tracer for subdermal injection, upper extremity injection sites, and interval between tracer injection and SPECT scanning. Recruitment has been somewhat slower than anticipated. Nonetheless 2-3 patients have been enrolled each month since recruitment began.

b. Data collection

Complete 12-month data has been collected on 2 subjects, six-month data on 13 subjects, and initial data on 30 subjects.

c. Institutional Review Board approval

Approvals for the study have been obtained and appropriately renewed from the USAMRMC Review Board, the University of Pennsylvania Institutional Review Board, and the Abramson Family Cancer Institute Clinical Trials Committee.

d. Data Entry

A Microsoft Access database has been constructed which includes subjects' sociodemographic and cancer treatment-related variables. The principal investigator is currently working with physicists from the Nuclear Medicine and Radiation Oncology Departments, as well as her co-investigators to determine the imaging and dosimetry variables that will most comprehensively and succinctly capture subjects' SPECT scan and radiation dosimetry results. The project research coordinator is currently expanding the database to include these variables, once determined.

e. Data Analysis

To date, data analysis has been restricted due to incomplete data collection. Preliminary descriptive statistics of cancer treatment related, SPECT scan and dosimetry results have been calculated for abstract submission. Thirteen subjects (43%) were Afro-American, 16 were Caucasian (53%), and one was Hispanic (3%). The relatively high proportion of Afro-American subjects reflects the diversity of the patient population treated at the University of Pennsylvania Health System. Fifty percent (15) of the enrolled subjects had sentinel lymph node dissections alone, while the other 50% underwent \geq 2-level surgical axillary clearing. Sixteen subjects (53%) had right-sided breast cancer. Thirteen subjects (43%) underwent modified radical mastectomies, while seventeen (57%) elected for breast conservation therapy. Thirteen patients (43%), a slightly different subgroup, received radiation to breast tangents while the remaining subjects received four field) irradiation tangents, posterior axillary boost, and supraclavicular fields).

The lymph node (LN) distribution was 1-10 with a mean of 3 LNs/patient distributed through out breast, axillary and supraclavicular LN beds. No lymph nodes were visualized in 2 patients (7.0%). Level I nodes were visualized in the lateral axilla in 62.5% of cases and in the medial axilla in 68.8% of cases. Level II/III nodes were detected in 50% of patients. Supraclavicular lymph nodes were visualized in 56.3% of cases. Dosimetry indicates that LNs draining the arm receive the full prescribed radiation dose (46 – 50 Gy) irrespective of location. Subjects who had undergone two-level axillary dissections were more likely to have >4 LNs identified on CT-SPECT ($p = 0.006$, X^2). This finding is very interesting from a physiological perspective. It has been long appreciated that roughly 40% of breast cancer patients who undergo aggressive treatment, e.g. modified radical mastectomy, full surgical axillary LN clearing, and four-field irradiation, do not develop lymphedema. Till now the reason(s) for the failure of patients with effectively no functioning lymphatics to develop lymphedema remained speculative. Our results suggest that collateral drainage pathways involving multiple LN are recruited after surgical removal of the LNs congenitally predisposed to drain the arm. This finding is clinically relevant since it supports the need to develop clinical strategies to enhance lymphatic collateralization during and after primary breast cancer treatment.

f. Manuscript Preparation

The results of this study are relevant to audiences from different medical disciplines including nuclear medicine, radiation physics and oncology, and lymphology. For this reason several manuscripts are planned. Two are currently being prepared. The first will report the lymph node mapping and SPECT scanning techniques utilized. This paper will be submitted to a nuclear medicine journal. The second will report the SPECT and simulation CT image fusion strategy used for quantification of radiation dosimetry.

Key Research Accomplishments

1. Development of mapping strategy to identify LN essential for arm drainage after surgical axillary LN removal for primary breast cancer.
2. Precise anatomic localization of LNs draining the arm using eINTEGRA SPECT scanning.
3. Fusion of eINTEGRA scans with CT simulation images used in radiation planning with the potential to develop individually tailored radiation fields that exclude or include pathophysiologically relevant LNs.
4. Accurate quantification of radiation dosimetry delivered to LN essential for arm drainage following surgical manipulation of the axillary LN bed (e.g. sentinel LN biopsy or 2-level axillary clearing).
5. Construction of individually tailored fields that minimize radiation exposure to the LNs draining the arm using conventional intensity modulated radiation therapy techniques.
6. Discovery of the first evidence to support lymphatic collateralization following removal of LNs congenitally predisposed to drain the arm.

Reportable Outcomes

1. Presentation of Grand Rounds to the Department of Physical Medicine and Rehabilitation at the Mayo Clinic, Rochester Minnesota. November, 2005.
2. Presentation of Grand Rounds to the Department of Physical Medicine and Rehabilitation at the Medical College of Wisconsin. June, 2006
3. Abstract accepted for a platform presentation at the American Society of Nuclear Medicine. June, 2006
4. Abstract submitted to the European Society of Therapeutic Radiation Oncology. If accepted, a platform presentation or poster will be presented in October, 2006.
5. Abstract submitted to the National Lymphedema Network. If accepted, a platform presentation or poster will be presented in November, 2006.

Conclusion

Work to date has demonstrated that LNs draining the arm after surgical manipulation of the axilla for treatment of primary breast cancer can be anatomically localized using eINTGRA SPECT scanning. The radiation dose delivered to these LNs can be precisely quantified by fusing the eINTEGRA SCECT images with the CT scans used for radiation simulation. With this information, individually tailored radiation fields can be constructed that minimize damage to LNs draining the arm. Individually tailored fields may be considered for patients with low risk breast cancers (e.g. small tumor, hormone receptor positive, benign histopathological characteristics, and negative sentinel LNs), and substantially reduce their risk of lymphedema. Additionally, the fact that subjects status post ≥ 2 -level surgical axillary clearing have more LNs visualized on SPECT scanning suggests that lymphatic collateralization is occurring and justifies the development of techniques to enhance this endogenous compensatory mechanism.

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Appendix A

Courses taken toward Masters Degree in Clinical Epidemiology

EPID 999 - Independent Study in Clinical Epidemiology

Instructor: [Andrea Troxel, ScD](#)

This is a preceptorship focused on the construction of generalized linear models for the analysis and categorical data.

EPID 999 - Independent Study in Clinical Epidemiology

Instructor: [Andrea Troxel, ScD](#)

This is a preceptorship focused on the construction of mixed and multilevel models for longitudinal data.

EPID 900 and EPID 990 - Masters Thesis

Instructor: [Angela DeMichele, MD, MSCE](#)

These are a series of tutorial sessions conducted by the student's advisor, which are to support the student's efforts in developing a research protocol, designing a research project, and completing the study.

EPID 992 - Dissertation Research

Instructor: [Angela DeMichele, MD, MSCE](#) and CCEB faculty

These are a series of tutorial sessions conducted by the student's dissertation advisor, which are to support the student's efforts in developing a research protocol, designing a research project, and completing the study.

EPID 634 - Clinical Trial Outcomes: Measurement, Analysis, and Interpretation

Instructor: [John Farrar, MD](#)

This course is intended to teach students the skills necessary to select and/or design appropriate outcomes for a clinical trial. Students will focus on recent changes in our understanding of clinical trial outcome measurements, analyses, and interpretation for both subjective and objective phenomenon, such as adherence, use of multiple outcomes, and clinical importance. While design issues for clinical trials are the main focus, other types of clinical studies will be considered as appropriate. Students will be expected to learn about the problems inherent in the design of outcome measures of health and how to apply different epidemiologic and biostatistical concepts toward a solution. It is expected that at the conclusion of the course, students will be able to plan a clinical trial with a valid, responsive and interpretable outcome. The class will meet once weekly for a 60 minute lecture on a topic, followed by a 60-90 minute discussion of how that topic applies to the specific issues of interest of the students or the instructor. Students will be evaluated on their participation in class (25%); a paper describing the application of one of the methods to an area of interest (50%); and a class presentation of their topic (25%).

EP 623 Survival Data Analysis

Instructor: [Scarlett Bellamy, ScD](#)

This course will focus on the specialized issues related to the analysis of survival or time-to-event data. The course begins by closely examining the features unique to survival data which distinguishes these data from other more familiar types. Topics include non-parametric survival analysis methods, common survival functions, parametric survival models, the proportional hazards model, and common model checking methods. All methods will be illustrated by in class examples and homework sets.

EP 622 Applied Regression Models for Categorical Data

Instructor: [Andrea Troxel ScD](#)

This course will provide in-depth treatment of several topics in categorical data analysis. After a brief review of methods for contingency tables, we will introduce the idea of generalized linear models, and focus on two special cases – multiple logistic regression and loglinear models. Each topic will be presented in detail by stating the model and covering parameter estimation and interpretation, inference, model building, regression diagnostics and assessment of model fit. Finally, we will cover extensions to both models, including models for multinomial data, analysis of matched-pair data, and random effects models. Topics will be illustrated in class with examples, and we will discuss the use of Stata to conduct the analyses.

EPID 570 - Critical Appraisal of the Medical Literature

Instructors: [Jason Christie, MD](#)

This seminar focuses on techniques for critical appraisal of the medical literature. Each student will be responsible for at least one critical appraisal session covering different epidemiologic topics (including the evaluation of diagnostic tests,

clinical course and prognosis of disease, disease etiology or causation, therapy, quality of clinical care, economic evaluation, and meta-analysis). For his/her session, each student will appraise critically a journal article and lead the discussion concerning that article.

EPID 560 - Issues in Research Protocol Development

Instructors: [Dennis Durbin, MD, MSCE](#)

This is a seminar that focuses on major issues in research protocol development, including methodological issues regarding different research designs, development of research questions, and plans for analysis. Each student will present his or her research proposal for open discussion during one of the seminar sessions.

EPID 550 - Clinical Economics and Clinical Decision Making

Instructors: [Sankey Williams, MD](#) and [Henry Glick, PhD](#)

This course focuses on the application of decision analysis and economic analysis to clinical and policy research. The course begins with material about the selection, use, and analysis of diagnostic tests using two by two tables, likelihood ratios, and ROC curves. The course continues with the introduction of more general tools for decision analysis, including decision trees and other mathematical models. Special emphasis is placed on the assessment and use of utilities in these models. A major focus of the course is the application of economic principles to the evaluation of health outcomes. During seminars, students will carry out practical exercises that include problem solving, critically analyzing published articles, and learning to use computer software that facilitates decision and economic analyses.

EPID 542 - Measurement of Health in Epidemiology

Instructor: [William Holmes, MD, MSCE](#)

This course is a series of lectures and discussion sessions designed to introduce the student to the concepts of health measurement as applied to epidemiologic studies. Topics covered include: the basics of health measurement theory; critical evaluation of the current status of health measurement in a chosen field; and techniques for developing and using measurement scales, including item analysis, validity and reliability testing, and qualitative methods.

EPID 532 - Database Management for Clinical Epidemiology

Instructor: [John Holmes, PhD](#)

This course provides students with an introduction to the techniques of database management as they apply to clinical research. Students learn how to design and implement computerized databases, perform basic query and reporting operations, migrate data between various file formats, prepare databases for statistical analysis, and perform quality assurance procedures. This course focuses on the practical issues of database management and is intended to support each student's planned research enterprise.

EPID 521 - Statistical Methods for Epidemiologic Research

Instructor: [Russell Localio, J.D., MA, MPH, PhD](#)

This seminar focuses on statistical methods for analyzing case-control, cross-sectional, and cohort studies, and clinical trials. Topics include simple analysis of epidemiologic measures of effect; stratified analysis; ordinary linear, logistic, and Poisson regression methods; simple survival analyses including Cox regression; power and sample size calculations; confounding interaction; and the use of matching. All methods are practiced on existing data sets. Six laboratory sessions focus on the use of statistical software in epidemiologic research.

EPID 510 - Introductory Epidemiology

Instructor: [James Lewis, MD, MSCE](#)

This course is a series of lectures and workshops, designed to teach basic principles of epidemiologic research design. The course provides an overview of the types of research questions that can be addressed by epidemiologic methods. Topics covered include: definitions of epidemiology; measures of disease frequency; measures of effect and association; epidemiologic study designs, both experimental and non-experimental; and an overview of analysis of epidemiologic studies.

EPID 502 - Fundamentals of Medical Research II: Introduction to Biostatistics

Instructor: [Warren Bilker, PhD](#)

This course is a series of lectures designed to provide an overview of the fundamental concepts of biostatistics. Topics covered include probability, estimation, confidence intervals, hypothesis testing including nonparametric techniques, correlation, regression, analysis of variance, and analysis of covariance. Emphasis will be placed on understanding the proper application and underlying assumptions of the methods presented. (The lectures for this course are the same lectures as for EPID 520.)

Appendix B

Dr. Cheville's approved thesis for masters degree in Clinical Epidemiology

Assessment of Rehabilitation Service Utilization Among Stage IV Breast Cancer Patients

Authors: Cheville AC, Troxel A, Kornblith A

Abstract

Problem statement:

Breast cancer-related impairments cause functional decline in patients with Stage IV cancer, yet rehabilitation services are not routinely integrated into the care of these patients.

Purpose:

The primary goals of this study were to: 1. quantify rehabilitation needs among Stage IV breast cancer patients; 2. determine the degree to which needs are being met; and 3. identify covariates associated with receipt of rehabilitation services.

Patients and methods:

A consecutive sample of 163 Stage IV breast cancer patients, stratified by Karnofksy Performance Scores, receiving parenteral chemotherapy was enrolled. Subjects were administered the Mental Health Inventory-17, the Medical Outcomes Study Physical Function Subscale, the Older Americans Resource Study Activities of Daily Living subscales, and the Brief Pain Inventory.

Cancer-related physical impairments were identified through a clinician-administered neurological and musculoskeletal examination, the Six Minute Walk Test, and administration of the Functional Independence Measure (FIM) Mobility Subscale. Subjects were questioned regarding receipt of rehabilitation services and hospitalization status for all impairments. Rehabilitation needs for each impairment were determined through a consensus process involving physiatrists, physical therapists, and occupational therapists specializing in cancer.

Results:

530 physical impairments were detected among 150 subjects, 484 (92%) required rehabilitation while 469 (88%) required physical (PT) or occupational therapy (OT). Seventy percent of impairments that required rehabilitation and 79% that required PT/OT were untreated.

Impairments that required hospitalization were overwhelmingly more likely to receive rehabilitation, OR 87.88 (95% CI 28.46 - 271.36), and PT/OT, OR 558.75 (95% CI 186.99 - 1669.61). Subject characteristics associated with low socioeconomic status were significantly associated with non-treatment of impairments. Caucasian subjects were more likely to receive rehabilitation, OR 2.99 (95% CI 1.40 - 6.42), and PT/OT, OR 5.68 (95% CI 2.18 - 14.82). When adjusted for hospitalization status, subject ethnicity, and socioeconomic covariates, functional status did not predict receipt of rehabilitation services.

Conclusion:

Rehabilitation services are severely underutilization among functionally compromised Stage IV breast cancer patients. Physical impairments that do lead to hospitalization, or occur in ethnic minorities and socioeconomically disadvantaged subjects are more likely to be untreated.

Virtually all patients diagnosed with Stage IV cancer will eventually experience significant functional deterioration (Lunney). Cancer-related physical impairments contribute to declining functional independence, which is a primary concern (Axelsson), and source of psychological distress for patients (Breitbart, O'Mahoney), as well as a critical dimension of their health-related quality of life (HRQOL) (Ganz, Cella). Physical impairments increase direct and indirect cancer treatment costs, and significantly increase caretaker burden (Kurtz, Radice). Given that cancer affects 45% (ACS) of the population, function in cancer patients, particularly those with Stage IV disease, has significant implications for public health, medico economic, and clinical decision making.

Breast cancer affects 12% of all women and 20% eventually develop metastatic, Stage IV, disease (ACS). Increasing treatment options and better symptom-oriented care (Levy, Miaskowski) offer the possibility of extended quantity and quality of life for patients with Stage IV breast cancer. Unfortunately, physical impairments pose a significant barrier to the realization of this potential. Rehabilitation services preserve function in many chronic, progressive diseases similar to cancer (Kraft, Yarasheske). However, rehabilitation services are not routinely offered to cancer patients (Conti, McAleer), and the literature describes a large qualitative gap between rehabilitation needs and available services (Lehmann). To date, neither rehabilitation need, nor service utilization have been quantified in a cancer cohort, nor has the prevalence of impairments related to breast cancer and its treatment been quantified. This lack of knowledge represents an obstacle to the implementation of care pathways that maximize function throughout the course of Stage IV breast cancer.

This cross sectional study was designed to address these issues among patients with Stage IV breast cancer. The study's goals were to determine: 1. the magnitude of rehabilitation need using the number of physical impairments that a patient may have as a surrogate for disability, and 2. whether physical impairments were treated with appropriate rehabilitation services. An additional goal was to identify patient, cancer and impairment characteristics that predicted receipt of rehabilitation services. It was hypothesized that access to rehabilitation services would depend on whether patients interfaced with established systems of rehabilitation care delivery. Physical and

occupational therapy are routinely offered to hospitalized patients. It was therefore hypothesized that a history of inpatient hospitalization would be associated with receipt of rehabilitation services

Methods

Subjects

A consecutive sample of Stage IV breast cancer patients receiving parenteral chemotherapy was enrolled at the Evelyn H. Lauder Breast Center at Memorial Sloan-Kettering Cancer Center (MSKCC). Subjects were enrolled in July and August, 1999.

Eligible subjects were required to have Stage IV breast cancer, be 18 years of age or older, have intact mental status, and be sufficiently fluent in English to complete the study instruments.

Disease status was determined by review of the electronic medical record (EMR), verbal communication with oncologists or clinical nurse specialists, and the presence of metastases on recent imaging studies. Potential subjects were approached prior to chemotherapy or parenteral bisphosphonate treatments, and invited to participate by the principal investigator (PI) or a research assistant.

Stratified sampling was utilized to ensure adequate representation of subjects with advanced disease. Three enrollment strata were planned based on subjects' Karnofsky Performance Scale (KPS) scores. KPS Scores ranging from 40-90 were collapsed into the following strata: 80-90, 60-70, and 40-50. The KPS is a single dimensional scale with values from 0 to 100 originally intended to be administered by caregivers (Schag). The KPS measures the extent to which cancer compromises patients' global functional status with higher scores indicating better function. Changes of 20% are usually considered to be clinically significant (O'Dell, 1995). There are almost no validation studies, but it has been used in a large number of clinical trials and has demonstrated clinically meaningful changes.

A total of 212 patients were screened for study participation. Thirty-one (14.62%) patients were ineligible due to insufficient fluency in English to complete the study questionnaire. Eighteen patients declined to participate. Relative to study participants, patients who were ineligible based on English fluency were more likely to be Asian (73% versus 2.5%). Otherwise ineligible patients

and those that declined to participate did not significantly differ on sociodemographic or cancer-specific variables. The final study sample consisted of 163 subjects with 72 in the KPS 80 - 90 stratum, 51 in the 60-70 stratum, and 40 in the 40-50 stratum.

Data Collection

Data were collected from four sources: the electronic medical record, clinician-administered physical testing, the study instrument, and a semi-structured patient interview. All data were collected on the same day. Subjects were given the option of having the study instrument verbally administered by the PI or a research assistant. Twenty-two percent of subjects elected to have the instrument verbally administered. These subjects did not differ significantly in sociodemographic or cancer-specific variables from subjects who completed the study instruments independently. After subjects completed the study instrument, the PI or a research assistant reviewed the instrument for incorrectly completed and missing responses. If present, these items were verbally re-administered to the subjects after sources of ambiguity and confusion were addressed.

Electronic Medical Record

EMR review: EMRs were reviewed by the principal investigator after administration of the study instrument and physical examination. The EMR contained data on all outpatient and inpatient treatments delivered at MSKCC. The EMR is a comprehensive document of patients' clinical status and treatment history as the subjects received all their medical care at MSKCC following diagnosis with Stage IV disease.

A systematic approach to record review was imposed by the use of a data collection form. Sociodemographic variables were recorded from the '*Demographics*' section of the EMR. This is updated during registration for each clinical encounter. Relevant dates, details of primary breast cancer treatment, and KPS score were obtained from oncology initial evaluations and follow-up notes. The electronic record was sequentially reviewed for history of chemotherapy treatments, radiation treatments, and cancer-related surgery. Sites of metastases were determined from oncology clinic notes and imaging reports.

Clinician administered physical testing

Physical examination: The PI performed a standard musculo-skeletal and neurologic examination. This included: assessment of neck, shoulder and hip range of motion using a goniometer and a cervical range of motion device (Ordway); palpation of cervical, thoracic, and lumbar perispinal, as well as shoulder and hip girdle muscles; testing of cranial nerves II – XII; manual strength testing of the major upper and lower extremity muscle groups; testing of sensation in dermatomal and peripheral nerve distributions; testing of upper and lower extremity deep tendon reflexes; tandem gait analysis; testing for dysmetria and dysdiadochokinesia; and measurement of upper and lower extremity limb circumferences. Complaints of pain or other adverse symptom led to immediate discontinuation of any provocative maneuvers.

6 minute walk: The 6 minute walk test (6MWT) measures the distance a subject covers while walking 6 minutes in a level 30m hallway. The 6MWT has well demonstrated validity and reliability (Guyatt, Rostagno). The subjects are instructed to walk as quickly as possible up and down the hallway for 6 minutes. Participants are given standard encouragement every minute. For example, “You are doing well, you have 5 minutes to go.” The total distance walked during the test was recorded to the nearest tenth of a meter. Subjects were asked to rate their shortness of breath after completion of the 6MWT on a 5-point Likert scale.

Functional Independence Measure Mobility Subscale: The FIM mobility subscale is a clinician-rated ordinal scale composed of 5 items including transfers, ambulation, and stair climbing among other functional tasks (Granger, 1993; Granger, 1990) The response set has 7 levels ranging from 1(total dependence) to 7 (total independence). The possible range for the entire FIM mobility subscale is from 5 to 35. The FIM mobility subscale has been demonstrated to be valid and with adequate discrimination in disabled cancer cohorts (Huang; O’Dell, 1998)

Self-report Study Instrument

Older Americans Resource Study (OARS): The OARS Social/Financial Resources, activities of daily living (ADL), and instrumental activities of daily living (IADL) subscales contain 15, 7, and 7 items, respectively (Fillenbaum). Individual items in the Social/Financial Resources subscale include between 5 and 14 response options that are specific to each item. For example, ‘Who lives with you?’ offers 11 possible responses and respondents are instructed to endorse all that apply.

The OARS ADL and IADL subscales assess respondents' capacity to perform basic and instrumental ADLs. IADLs include use of the telephone, traveling, shopping, preparing meals, etc Autonomy in ADL and IADL performance is rated between 1 and 3 (1=without any help, 2=with some help, 3=completely unable). Scores for the ADL and IADL items are collapsed to 'independent'=1 and 'some difficulty'=0, and then summed for each subscale. The sums are converted to 4-point Likert scales (7=No problems, 4-6 ADL problems=Mild, 2-3 problems=Moderate, 0-1=Severe). The OARS ADL and IADL subscales have been shown to be responsive and discriminative in cancer cohorts (Kornblith, Bailey).

Physical Function-10: The PF-10 is one of twelve general health concepts included in the Medical Outcome Study 149-Item Functioning and Well-Being Profile (Stewart) and one of eight in the Short Form-36 Health Survey (Ware). The PF-10 consists of ten self-report items that assess the extent of health-related limitations in a variety of physical activities including walking, climbing stairs, lifting or carrying groceries, etc. Each item is scored between 1 and 3 (1=limited a lot, 2=limited a little, 3=not limited at all). The algebraic sum is computed and transformed into a 1-100 scale, with 100 indicating the most favorable level of physical functioning, 0 the least favorable, and scores in between representing the percentage of the total possible score achieved. The PF-10 has been widely used and validated in disabled and chronically diseased populations (Stewart).

Brief Pain Inventory: The Brief Pain Inventory (BPI) consists of 15 items that assess the location of pain, its severity, the degree to which it interferes with daily activities, and extent of pain relief from analgesics (Daut, Daut). All items except those concerning pain location and medications consist of 11 point visual analogue scales, ranging from 0 to 10. Pain intensity items are rated on this scale from 'no pain' to 'pain as bad as you can imagine.' Pain's interference with activity items (e.g. mood, relations with other people, walking) are rated on a scale from 0 to 10, 'does not interfere' to 'completely interferes.' Higher scores for all items and subscales indicate worse pain. The BPI has been widely used and validated in cancer populations (Cleeland).

Mental Health Inventory-17: The MHI-17 (Stewart) is a brief version of the original Mental Health Inventory from the Medical Outcomes Study (Ware) measuring psychological state,

consisting of 17 items grouped into the following five subscales, two global subscales and a total score: anxiety, depression, positive affect, emotional ties, loss of behavioral and emotional control, global psychological distress, positive affect and the MHI Index (total score). Response options are in the form of a six point Likert scale, from ‘none of the time’ to ‘all of the time.’ Scores are transformed to a 0-100 scale, with higher scores on the MIH Index indicating a better emotional state.

Structured Interview

Rehabilitation service utilization: Scripted questions were used to elicit information regarding rehabilitation service utilization for each impairment identified on clinical examination. Patients were asked separate questions about receipt of specific therapy services, e.g. physical therapy (PT) and occupational therapy (OT). Examples of typical therapy treatments were provided to facilitate recall. Subjects were questioned about receipt of assistive devices for mobility (e.g. standard cane, walker) and ADL performance (e.g. reachers, grabbers), as well as orthotics and compression garments. Photographs of typical items in each of these categories were used to facilitate recall.

History of hospitalization: Subjects were asked, “Were you ever admitted to the hospital for this problem,” regarding each impairment identified on clinical examination.

Post-examination EMR review, subject evaluation, and rehabilitation need determination

Identification of impairments: An *a priori* list of impairments that would be screened was not generated. However, the range of potentially detectable impairments was implicit in the components of the physical examination. These included musculoskeletal (e.g. contractures, myogenic weakness, myofascial dysfunction), neurological (e.g. myelopathy, cranial neuropathy), and cardio- and lympho-vascular deficits (e.g. cardiopulmonary deconditioning, lymphedema). Identification of all impairments and some of their etiologies was based on physical examination findings, the Six Minute Walk Test, and administration of the FIM mobility subscale. Etiological determination was supplemented with information in the oncology clinic notes, as well as consultant, imaging, operative, and other diagnostic test reports. Impairments with no explanation in the EMR were brought to the attention of the treating oncologist by the PI on the day of data collection. The causes of such ‘new’

impairments were investigated through diagnostic workup, e.g. appropriate imaging studies, electromyograms, etc. Initiation of a diagnostic workup was required for <5% of impairments. Several impairments were attributed to deconditioning by default. For example, if generalized strength deficits were detected on clinical examination that did not conform to a neuropathic or myopathic pattern, they were attributed to deconditioning. Similarly, moderate to severe dyspnea following the 6MWT was attributed to aerobic deconditioning in the absence of known cardiac or pulmonary pathology.

Determination of rehabilitation need: The PI, a board-certified Physical Medicine and Rehabilitation (PM&R) physician specializing in cancer, assessed whether and what type of rehabilitation services were required once a patient's data set was complete. A determination of need was made for each impairment in six *a priori* defined rehabilitation service categories. These categories included: 1. assistive device for ADL performance, 2. assistive device for mobility, 3. orthotic, 4. compression garment, 5. PT, 6. OT. Treatment status was coded in each category as "needs," "doesn't need," "received," or "received and still needs." Determinations were based on conventional PM&R practice. Subjects with multiple impairments received separate determinations of rehabilitation needs for each impairment. The PI applied impairment-specific treatment standards when available. For example, a white paper generated by the International Society of Lymphology offers clear guidelines regarding the management of lymphedema (Bernas). Decisions for impairments lacking definitive treatment standards were based on recommendations outlined in rehabilitation medicine texts (Braddom, DeLisa) as well as in PT and OT manuals. The potential benefits of patient education; family training; prevention of further functional and medical morbidity; and proactive management of progressive impairments were considered in determinations of rehabilitation need. The PI's determinations were independently reviewed by a second PM&R physician specializing in cancer. Conflicting assessments of rehabilitation requirements were resolved through a consensus process involving the PM&R physicians, as well as physical and occupational therapists specializing in cancer.

To simplify the statistical analysis, the response set was collapsed to a binary variable "needs" versus "received." If an impairment had ever received treatment in a given category, irrespective of current need, it was coded "received." Untreated impairments that required rehabilitation were

coded “needs.” The rehabilitation treatment categories were collapsed to ‘rehabilitation’ and ‘therapy’ in order to further simplify the analysis; i.e., if an impairment had been addressed with any type of rehabilitative intervention (e.g. assistive device, orthotic, garment, therapy, etc.) it was coded ‘received rehabilitation.’ No distinction was made between treatments initiated independently by subjects versus by physician referral. In contrast, the designation ‘received therapy,’ indicated that an impairment had been addressed with PT or OT. A physician’s prescription is required for PT and OT, and insurance coverage can be complex. Therefore, receipt of ‘therapy’ versus ‘rehabilitation’ is subject to different physician-based, institutional, economic, and insurance determinants. We judged the determinants sufficiently distinct to warrant separate analyses.

Statistical Analysis

The sample size and proportions of patients who received rehabilitation or therapy were fixed by design. Power calculations with a two-sided α of .05 indicate that we have $> .8$ power to detect differences in proportions $\geq .14$ and $\geq .16$ when groups are defined by receipt of rehabilitation and therapy, respectively. That is to say, there is $< 20\%$ chance of a β -type error when the difference in inter-group prevalence is $\geq 14\%$ or $\geq 16\%$, depending on how the groups are defined. For continuous variables, we have 80% power to detect an inter-group difference of .28 standard deviations. For example, the mean age is 57.66 with a standard deviation of 11.80. We could therefore detect an inter-group difference of 3.29 years with 80% power.

Descriptive statistics for the total sample, as well as for KPS-based strata, were calculated for subject-level variables, Table 1. The presence of a progressive decrease or increase across KPS strata was assessed with linear regression for continuous variables, the X^2 test for categorical variables, and with a nonparametric test for trend across ordered groups (Cusick) (an extension of the Wilcoxon rank-sum test) for ordinal variables. Descriptive statistics were also calculated for impairment-level data, Table 2. Impairment-level variables included the prevalence of impairment sub-types, whether impairments necessitated hospitalization, and whether impairments were associated with an orthopedic procedure. X^2 tests were performed to determine whether the proportions of impairments treated with rehabilitation or therapy differed by impairment sub-type and characteristics.

The data include subject-level (e.g. demographic and disease-related specifics unique to each subject), as well as impairment-level variables (e.g. type of impairment and rehabilitation needs). The information presented in Tables 1 and 2 are subject-level and impairment-level, respectively. The majority of subjects had more than one physical impairment, and as a whole the group displayed a mean of 3.28 (SD 1.99) impairments/subject. For example, among 62 subjects with arm lymphedema, 17 also had neurogenic weakness from peripheral nervous system pathology and 19 had severe exertional intolerance from deconditioning. Data analysis at the subject-level (e.g., had subjects received rehabilitation or therapy) without distinction between separate impairments would result in a subject being coded as receiving rehabilitation if they received any intervention despite the fact that additional impairments may have been untreated. For this reason, we used ‘receipt of rehabilitation’ and ‘receipt of therapy’ at the impairment-level as the dependent variables in the logistic regression analyses, which were adjusted for clustering within subjects. Independent covariates in the regression models were both impairment- and subject-level.

Univariate logistic regressions were performed with receipt of rehabilitation and receipt of therapy, at the impairment-level, as the dichotomous outcome variables to assess their association with the 29 sociodemographic (subject-level), 9 cancer-related (subject-level), 7 function-related (subject-level), 2 symptom-related, and 19 impairment-specific variables, Table 3. One-to-many relationships existed between most subjects and their impairments, with a single subject having multiple impairments and therefore contributing multiple observations to the dataset. The models were adjusted for clustering of impairments within subjects. The covariate with the most significant Wald statistic and highest log likelihood in the univariate logistic regressions was incorporated into the next analytic step; bivariate logistic regressions. This procedure was applied to serial models with increasing numbers of covariates. Covariates at each step of model construction with the most significant Wald statistics and highest log likelihoods were retained. Covariates were eliminated for P values >0.05 . This procedure was repeated until no additional covariates could be included in the model with P values ≤ 0.05 .

To test the stability of our final models, backward and bidirectional stepwise logistic regressions were used to determine whether the resultant models would differ from our final models. $P \leq 0.05$

was used for inclusion and $P > 0.06$ for elimination. These alternative strategies resulted in differences in a few variables, but when these variables were included in the final models they failed to meet our retention criteria of $P \leq 0.05$. Interaction terms were tested based on effects noted in the literature and potential mechanistic links. Likelihood ratio tests failed to detect interaction effects. Potential collinearity was assessed by evaluating the effect of selectively removing covariates from the model on β coefficients and Wald statistics. Model diagnostics were performed and all influential observations checked for data accuracy. The final model was assessed using the Hosmer-Lemeshow goodness-of-fit test with 10 groups (Hosmer) which indicated no evidence of lack of fit: ‘received rehabilitation’, $P=0.97$; ‘received therapy’, $P=0.89$.

We assessed the predictive accuracy of the final model by assessing discrimination with receiver operating characteristic curves (Metz). Odds ratios (ORs) are presented with their corresponding 95% confidence intervals, Tables 4 and 5, and significance was assessed using Wald tests. A p-value less than or equal to 0.05 was considered to be statistically significant, all tests were 2-tailed. All statistical analysis was performed with STATA for Windows, version 8.0.

Results

Study patients

Sociodemographics: A total of 163 patients were enrolled. The KPS-based stratified sampling approach failed to yield balanced strata due to: 1. Absence of the most recent KPS scores in the EMR, 2. Termination of enrollment due to grant closure. When KPS scores were updated to reflect the date of data collection, the adjusted strata were imbalanced. The final study cohort contained overrepresentation of subjects with high KPS scores (KPS 89-90, N = 72 subjects; KPS 60-70, N = 51 subjects; KPS 40-50, N = 40). Demographic, clinical, and functional characteristics at the time of enrollment are presented in Table 1. Because this study used a stratified consecutive sampling plan, the estimates we present are based on data enriched for lower KPS scores and do not reflect prevalence rates among all Stage IV breast cancer patients.

All patients were female with a mean age of 56 years. The majority were married (52.76%) and lived with their husbands (52.15%). Half were retired (50.62%) with 20.99% receiving disability. Twenty two percent were unemployed. Most were Caucasian (70.55%). Ethnic minorities were

represented with the following frequencies: African American 19.02%, Hispanic 7.98%, and Asian 2.45%. Subjects with lower KPS scores were more likely to be retired on disability. They were also less likely to live with their husbands and to be working

Cancer characteristics: All patients had distant breast cancer metastases and were receiving parenteral therapy. The mean interval since diagnosis with Stage IV disease was 30.3 months (SD 27.4). Subjects had received an average of 3.17 (SD 2.05) different anti-cancer regimens including current treatment since Stage IV diagnosis. A majority of subjects (51.54%) had more than two metastatic sites. The most common site was bone (80.37%), followed by lung (53.99%) and liver (53.99%). Approximately half the subjects (46.63%) had received radiation for metastases. Just over one third (39.26%) underwent surgery related to Stage IV breast cancer. Subjects with lower KPS scores were more likely to have developed bone, liver, and lung metastases, and to have received a greater number of different treatment regimens. They were also more likely to have undergone radiation and surgery related to their breast cancer.

Function and symptom burden: Most subjects had significant physical dysfunction. Physical impairments were identified in 92% (150) of the study sample. Eighty eight percent required rehabilitation and therapy, though not necessarily for the same impairments. Only half (52.76%) the subjects had full strength in all muscles. Subjects had low PF-10 scores (mean 47.02, SD 31.72). Many subjects had difficulty with at least one ADL (42.94%) and IADL (73.62%). Significant self-care dysfunction, difficulty in ≥ 4 activities, was found 23.95% and 47.24% of subjects for ADLs and IADLs, respectively. FIM-mobility subscale scores (mean 30.17, SD 5.81) revealed that, on average, subjects were compromised in basic mobility. Moderate generalized disability, defined as FIM mobility subscale score < 30 , PF-10 < 35 , and ≥ 4 problems with instrumental ADLs (Stineman), was present in 53 (32%) subjects. Patients with lower KPS scores had significantly poorer physical function in all parameters. Although Brief Pain Inventory scores were higher among patients with greater functional morbidity, VAS “average” pain levels were low (mean 2.59, SD 2.51).

Less than half of the entire study sample (48%) had received rehabilitation. Seventy one subjects (49.31%), of the 144 who required rehabilitation, had not received a function-oriented intervention.

Among subjects requiring PT or OT, 87 (60.84%) had not been treated. Undertreatment was common in subjects with moderate disability; 30.19% (16) had not received rehabilitation and 58.49% (31) had not received PT or OT.

Impairments

530 impairments were diagnosed among the 163 subjects. Figure 1 presents the relative frequencies of different impairments in the study sample. On average, subjects had greater than 3 distinct physical impairments (mean 3.28, SD 1.99). In 13 subjects no impairments were detected. Table 2 presents impairment characteristics and categories, as well as the percentage that were addressed with rehabilitation or therapy. A rehabilitation intervention was indicated for 484 (91.32%) of the 530 impairments, with 469 (88%) requiring PT or OT. Thirty percent of impairments for which rehabilitation was indicated had been addressed with an intervention, and only 21.11% (99) impairments with a therapy indication had received PT or OT. Among the 246 impairments that were present in moderately disabled subjects, 63.82% were untreated.

Impairments were far more likely to receive a function-oriented intervention if they resulted in hospitalization. Sixty eight impairments (12.83%) resulted in hospitalization; 94.12% of impairments that required both hospitalization and rehabilitation were treated, while 89.71% of impairments that required both hospitalization and therapy were treated. Among impairments that did not lead to hospitalization and required treatment, only 19.47% received rehabilitation and 9.45% received therapy. Arm lymphedema, in this subset of 462 impairments, was treated most often; 35.80% received rehabilitation and 78.95% received therapy. The vast majority of remaining impairments (e.g. non-arm lymphedema) that did not require hospitalization were untreated; 85.31% did not receive rehabilitation and 97.65% did not receive therapy. Impairments related to an orthopedic procedure (e.g. arthroplasty, medullary rodding, spinal decompression, joint mobilization) were also more likely to receive rehabilitation. Among orthopedically induced impairments, 85.19% received rehabilitation and 70.37% received therapy. Impairments generally occurred more frequently in subjects with lower KPS scores. Significant inverse correlations were found between the prevalences leg lymphedema, hemiplegia, myelopathy, ataxia, and cranial nerve dysfunction and KPS scores.

Logistic regression analyses

Receipt of rehabilitation: Hospitalization status, at the impairment level, was mostly strongly associated with receipt of rehabilitation among the covariates included in the univariate logistic regressions, Table 3. Subject- and impairment-level covariates significantly predicted whether impairments requiring rehabilitation were addressed with a function-oriented intervention, Table 4. The model correctly predicted rehabilitation utilization for the majority of impairments with a C statistic of .8515. Hospitalization status was the strongest predictor of receipt of rehabilitation in the multiple logistic regression model with an odds ratio of 87.9 (95% CI 28.46 – 271.36). Impairments that required an orthopedic procedure were also much more likely to receive rehabilitation (OR 10.1, 95% CI 4.59 – 22.30). Arm lymphedema was more often addressed relative to other impairments (OR 7.2, 95% CI 3.61 – 14.43). Subject-level socioeconomic and ethnic covariates also predicted receipt of rehabilitation. Subjects receiving unemployment benefits (OR 0.21, 95% CI 0.10 – 0.41), or who identified themselves as “unemployed and seeking work” (OR 0.05, 95% CI 0.02 – 0.13) were more likely to have untreated impairments. Caucasian subjects were more likely to have received treatments for their impairments (OR 2.99, 95% CI 1.40 – 6.42).

Receipt of therapy: Hospitalization status was mostly strongly associated with receipt of therapy among the covariates included in the univariate logistic regressions, Table 3. Similar subject- and impairment-level covariates were associated with receipt of PT or OT in the multiple logistic regression model, Table 5. The full model correctly predicted receipt of therapy for the majority of impairments with a C statistic of .9598. Impairments that required hospitalization were overwhelmingly more likely to be addressed by a therapist (OR 558.7, 95% CI 186.99 – 1669.61). Arm lymphedema was more likely than other impairments to be referred for therapy (OR 69.59, 27.53 – 175.93). Impairments occurring in retired subjects on disability were also more likely to receive therapy (OR 2.8, 1.04 – 7.77). Subjects’ ethnicity predicted receipt of therapy. Caucasians’ impairments were more often treated (OR 5.7, 95% CI 2.18 – 14.82).

Once adjusted for the covariates listed in Tables 4 and 5, subjects’ functional status did not predict whether their impairments received rehabilitation or therapy. The Wald statistics associated with

impairment number, limb strength, PF-10 scores, OARS ADL and IADL subscale scores, and FIM scores were not significant in either logistic regression model.

Discussion

This study revealed underutilization of rehabilitation services among functionally compromised Stage IV breast cancer patients. Access to inpatient rehabilitation services was the strongest predictor of treatment. However, socioeconomic variables were also highly predictive.

Rehabilitation needs were significant among the sample of 163 subjects. Physical impairments were identified in 150 (92%) subjects, and 144 subjects (88%) required some type of rehabilitative intervention. Five hundred and thirty distinct physical impairments were identified in the sample, of which 484 (92%) required rehabilitation and 469 (88%) required PT or OT. The majority of impairments occurred in subjects with significant global functional decline (FIM mobility subscale score < 30, PF-10 < 35, and ≥ 4 problems with instrumental ADLs), indicating that impairments negatively affected multiple domains. Significant underutilization of rehabilitation was detected in the study sample. Half the subjects who required rehabilitation, and over 60% who required therapy had not been treated. Failure to receive rehabilitation was noted among subjects with very poor functional status. Sixty percent of subjects with significant global functional decline, as defined above, had not received PT or OT. The majority of subjects' physical impairments were untreated; specifically, 70% that required rehabilitation and 79% that required therapy had not received an intervention. Impairments in subjects with significant global functional decline were generally untreated (64%). Socioeconomic characteristics predicted receipt of rehabilitation services. Ethnic minorities were significantly less likely to receive rehabilitation or therapy. The relative odds of receiving rehabilitation and therapy were 3 and 6 times higher, respectively, for Caucasians relative to minorities. Unemployed subjects who were receiving benefits or looking for work were less likely to be treated. Physical impairments that led to hospitalization were strikingly more likely to receive rehabilitation (OR 88) and therapy (OR 559). Arm lymphedema and impairments associated with orthopedic procedures were also more likely to be treated.

To our knowledge this is the first study to quantify functional status, rehabilitation need, and rehabilitation utilization in a cancer cohort. In addition, we report the first description of subject and impairment characteristics that predict receipt of rehabilitation services. Our results differ

from previous studies of rehabilitation utilization among cancer patients in that they are quantitative and restricted to a specific cancer type and stage. Prior reports lack estimates of subjects' functional status, and impairment types and prevalences (Lehman, Mcaleer). The ecological design of many studies precludes identification of subject and impairment characteristics associated with rehabilitation service utilization (Conti, Lehman). Our study design permitted evaluation of such associations and revealed a dramatic and previously unreported disparity between the delivery of rehabilitation services in the outpatient and inpatient settings. Possible explanations for the magnitude of this finding are discussed below. Capture of subject-level information revealed the presence of racial and economic disparities in rehabilitation service utilization. Similar disparities have been reported for other types of cancer care (Griggs, Jatoi 2003, Jatoi 2005). Our findings also agree with reports that have described high impairment prevalences among breast and head and neck cancer patients following primary therapy (Karki, Olson), as well as among patients with advanced cancer (Lunney). In addition, significant undertreatment of symptoms and 'non-oncological' problems such as pain and depression has been noted in other cancer cohorts (Cleelend, Stiefel).

Our data were collected 6.5 years previous to preparation of this manuscript. The extended interval between data collection and publication raises uncertainty as to the current relevance of our findings. Although a legitimate concern, the principles of Stage IV breast cancer treatment have not changed significantly over this period aside from more frequent use of Herceptin (O'Shaughnessy). However, it is conceivable that minor modifications such as altered dosing strategies could influence impairment prevalences and severities. There has neither been an increase in the availability of cancer rehabilitation specialists (AAPMR, APTA), nor an indication of a trend toward greater integration of rehabilitation services into cancer care. The National Comprehensive Cancer Network's consensus Guidelines on Supportive Cancer Care do not mention rehabilitation (NCCN). Given the lack of intervening change in Stage IV breast cancer treatment and cancer rehabilitation, our findings are likely a reasonable approximation of current rehabilitation need and use among breast cancer patients.

Two principal sources of bias threaten the validity of our results. The most likely source of systematic misclassification bias by physiatrists would be over-interpretation of need for

rehabilitation. This would increase the estimate of under-utilization. However, the high rate of functional morbidity in the study cohort argues that rehabilitation was legitimately indicated for the majority of subjects. If only impairments occurring in subjects with significant functional compromise (FIM mobility subscale score < 30, PF-10 < 35, and ≥ 3 problems with instrumental ADLs) are considered, undertreatment rates do not change significantly; 63.5% of impairments did not receive rehabilitation, and 80.8% did not receive therapy. Of greater concern is the potential for subject recall bias with respect to receipt of rehabilitation and the impairment hospitalization status. Strategies to minimize recall bias included use of scripted questions during patient interviews, as well as use of photos of assistive devices, orthotics, garments, and PT/OT service delivery in a neutral setting (i.e. not in a hospital). It is possible that interviewers inadvertently encouraged patients to recall being hospitalized for treated impairments. This would bias the OR for impairment hospitalization status away from the null. However, only 12% (64) of impairments were both treated and required hospitalization. These impairments were distributed among 28 subjects, all but 4 of whom had treated impairments for which they did not recall being hospitalized.

Our sample differed in several ways from the target sample of all stage IV breast cancer patients. The study sample was deliberately enriched for functionally compromised subjects with lower KPS scores. Estimates for the total sample (Table 1) would therefore not apply to populations with KPS scores different from the distribution seen here. Strata-specific estimates would be more accurate. The study sample included breast cancer patients receiving parenteral chemohearpy. Although it is currently unknown whether patients treated with parenteral chemotherapy have more prevalent or severe physical impairments, it is reasonable to theorize that they may be more functionally compromised. The patients treated at MSKCC's Evelyn H. Lauder Breast Center may differ from other Stage IV breast cancer populations with respect to insurance coverage and economic status. The ethnic composition of the study was comparable to Manhattan's, although the 71% prevalence of Caucasians is higher than that found in greater New York City and the United States. In addition, patients who receive cancer care at urban, academic, quaternary cancer centers like MSKCC may differ in sociodemographic, clinical, and psychological respects from patients treated in community-based hospitals and private practices.

Institutional characteristics may have influenced our findings and constrain their generalizability to other practice settings. MSKCC does not offer outpatient rehabilitation services, with the exception of therapy for arm lymphedema. Patterns of outpatient service utilization at MSKCC may therefore differ from free standing cancer centers that offer outpatient rehabilitation services and from cancer centers housed within medical centers offering comprehensive rehabilitation services. Of note, arm lymphedema was more likely than any other physical impairment to receive rehabilitation (OR 7.2) or therapy (OR 69.6). This finding suggests that on-site availability of rehabilitation services may significantly influence utilization by patients and clinicians.

The associations between particular subject and impairment characteristics and receipt of rehabilitation services are strong (Tables 4 and 5). The magnitude of the effects suggests that they reflect important dimensions of rehabilitation service utilization among cancer patients. The most noteworthy finding is the overwhelming association of impairment hospitalization status with receipt of rehabilitation (OR 87.9) and therapy (OR 558.8). The reasons for this finding must remain speculative. Hospitalizations can be associated with sentinel, functionally catastrophic events (e.g. pathologic fractures, malignant spinal cord compressions) that precipitously alter patients' status and render them unable to function independently without rehabilitation. This fact does not explain the higher rate of in-hospital treatment of non-catastrophic impairments such as generalized muscle weakness, shoulder contractures, and exertional intolerance. Hospital-based rehabilitation services are commonly consulted when patients are potentially or grossly unsafe for home discharge. Such consultations result in a PT, OT, or physiatric evaluation for safety determination, for assessment of post-discharge rehabilitation needs, and to meet transfer facilities' admittance criteria. Rehabilitation services may also be automatically involved through critical pathways and standing post-operative orders. The latter may partially explain the high relative odds (10.1) of receiving rehabilitation for impairments associated with an orthopedic surgical procedure. Lastly, cancer patients are frequently discharged with visiting nurse services who can involve home PT and OT if patients are unable to safely negotiate their home environments (Freiman). The fact that rehabilitation was delivered for 94.1% of impairments requiring hospitalization reflects the effectiveness of hospital-based mechanisms for identifying rehabilitation need.

Only 19.5% of impairments that did not require hospitalization received rehabilitation, and 9.5% received therapy. Subjects with non-hospitalized impairments were, on average, functionally debilitated (e.g. PF-10<50). The low rate of treatment among these subjects, despite their poor functional status, may reflect the presence of cumulative, “minor” impairments, none of which caused sufficiently acute functional decline to trigger involvement of rehabilitation services. The distribution of impairment subcategories differed significantly between hospitalized and non-hospitalized impairments. Criteria do not currently exist to indicate when rehabilitation services should be involved in the care of Stage IV breast cancer patients. The low treatment rate among non-hospitalized impairments may also reflect the presence of geographic, financial, and logistical barriers. Cancer outpatients confront travel time and costs, co-payments, capitation to distant care and equipment providers, lapses in insurance coverage, complex pre-certification procedures and large initial out-of-pocket supply payments. Employment- and income-related variables strongly predicted receipt of service. These variables may reflect the adequacy of subjects’ insurance coverage. Retired subjects receiving disability were more likely to receive therapy (OR 2.9). Medicare insures the majority of patients receiving social security disability. Medicare fully covers all outpatient PT and OT services without pre-certification or co-payment. Further, Medicare does not capitate patients to specific therapy sites. The higher rate of therapy utilization by this group may reflect the absence of logistical and financial barriers.

The low prevalence of rehabilitation services utilization by the study sample is unfortunate since there are empiric and theoretical grounds for believing that Stage IV breast cancer patients can benefit from standard rehabilitative treatments. Many of the impairments caused by cancer or cancer therapy commonly occur in the absence of systemic disease (e.g. frozen shoulder, lymphedema) (Cheville). An extensive literature attests to the efficacy of standard physical and occupational therapy in treating these impairments (Bostrom, Foldi, Ko). Progressive and morbid systemic diseases do not meaningfully attenuate the benefit of these therapies. Patients with highly morbid conditions including lupus, multiple sclerosis, rheumatoid arthritis, and AIDS routinely benefit from rehabilitation (Hicks, Kraft, Yarasheske). Limited case series have described successful inpatient rehabilitation of Stage IV cancer cohorts using an integrated approach including physical, occupational, and speech therapies (Huang; O’Dell, 1998). More extensive literature describes the ability of patients receiving chemotherapy to benefit from standard aerobic

conditioning protocols (Courneya, Dimeo, 1997; Dimeo, 1999; Winnigham). These reports, coupled with the fact that highly morbid cohorts improve with rehabilitation, argue that there is nothing inherent in cancer, its treatment, or the presence of systemic disease to prevent patients from making substantial functional gains through rehabilitation.

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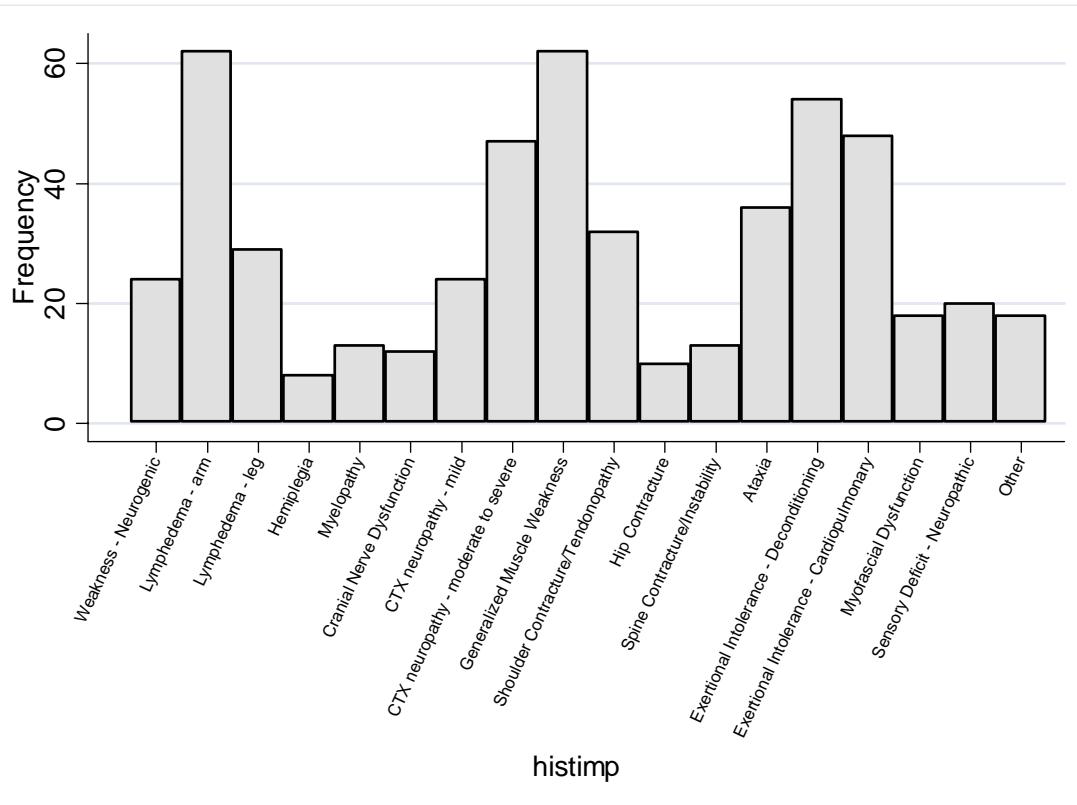


Figure 1. Frequencies of impairment subcategories in the study sample

Subject Characteristics		Cumulative Mean	SD	KPS 80-90 Mean	SD	KPS 60-70 Mean	SD	KPS 40-50 Mean	SD	P*
N (% total sample)	163									
Age	56.17	12.04	53.92	11.48	57.53	10.60	58.50	14.17	NS*	
Ethnicity	Caucasian	70.55% (115)		75% (54)		64.71% (33)		70% (28)		NS†
	Afro American	19.02% (31)		15.28% (11)		25.49% (13)		17.5% (7)		
	Asian	7.98% (4)		1.39% (1)		3.92% (2)		2.5% (1)		
	Hispanic	2.45% (13)		8.33% (6)		5.88% (3)		10% (4)		
Marital Status	single (never married)	16.56% (27)		11.11% (8)		19.61% (10)		22.50% (9)		NS†
	married	52.76% (86)		65.28% (47)		45.10% (23)		40.00% (16)		
	widowed	9.82% (16)		6.94% (5)		7.84% (4)		17.50% (7)		
	divorced	13.50% (22)		9.72% (7)		21.57% (11)		10.00% (4)		
	separated	7.36% (12)		6.94% (5)		5.88% (3)		10.00% (4)		
Live	Alone	19.63% (32)		15.28% (11)		19.61% (10)		27.50% (11)		0.13‡
	With husband	52.15% (85)		65.28% (47)		45.10% (23)		37.50% (15)		<0.001‡
	Other family	28.22% (46)		19.44% (14)		35.29% (18)		35% (14)		NS‡
Employment status§	Full-time	30.24% (49)		47.22% (34)		15.68% (8)		17.94% (7)		0.01‡
Working	Part-time	8.02% (13)		12.50% (9)		5.88% (3)		2.56% (1)		0.054‡
Unemployed		22.70% (37)		27.78% (20)		17.65% (9)		20.00% (8)		NS‡
Retired	No Disability	29.63% (48)		22.22% (16)		39.22% (20)		30.77% (12)		NS‡
	Disability	20.99% (34)		9.72% (7)		29.41% (15)		30.77% (12)		0.004‡
Student		1.2% (2)		0		3.9% (2)		0		NS‡
Stage IV at diagnosis		26.38% (43)				23.53% (12)		22.50% (9)		NS‡
Duration Stage VI (months)		30.33	27.4	23.27	22.7	37.77	31.6	33.56	27.07	NS‡
Metastatic sites	1 to 2	48.46% (79)		62.50% (45)		45.09% (23)		27.50% (11)		<0.001‡
	>2	51.54% (84)		37.50% (27)		54.90% (28)		72.5% (29)		
Location§	Bone	80.37% (131)		69.44% (50)		86.27% (44)		92.50% (37)		<0.001‡
	Liver	53.99% (88)		45.83% (33)		56.86% (29)		65.00% (26)		0.05‡
	Lung	53.99% (88)		47.22% (34)		54.90% (28)		65.00% (26)		NS‡
	Brain	11.04% (18)		4.17% (3)		11.76% (6)		22.50% (9)		<0.001‡
Number different treatment regimens		3.17	2.05	2.35	1.66	3.69	2.08	3.98	2.14	<0.001*
Radiation therapy	No	53.37% (87)		75% (54)		49.02% (25)		20% (8)		<0.001‡
	1	25.77% (42)		18.06% (13)		27.45% (14)		37.5% (15)		
	≥2	20.86% (34)		6.94% (5)		23.53% (12)		42.5% (17)		
History of cancer-related surgery(ies)		39.26% (64)		18.06% (13)		41.18% (21)		50% (20)		0.005‡
MHI-17	(0 - 100)	68.57	18.55	72.52	14.17	70.49	19.60	59.00	21.08	<0.001*
Pain VAS "average	(0 - 10)	2.59	2.51	1.50	2.05	3.36	2.53	3.58	2.52	<0.001*

pain"								
Number physical impairments	3.28	1.99	1.75	1.22	3.9	1.42	5.25	1.55
PF-10 (0 - 100)	47.02	31.72	72.71	22.39	36.57	20.77	14.13	15.56
Normal Strength	52.76% (86)		83.33% (60)		37.25% (19)		17.5% (7)	
≥4 IADL problems	47.24% (77)		15.28% (11)		56.86% (29)		92.50% (37)	
≥4 ADL problems	23.93% (39)		1.39% (1)		15.69% (8)		75.00% (30)	
FIM mobility (0 - 35)	30.17	5.81	34.51	1.28	29.98	3.66	22.58	5.12
Moderate disability^f	32.32% (53)		0		33.33% (17)		90.00% (36)	
For any impairment:								
needed rehabilitation	88.34% (144)		73.61% (53)		100.00% (51)		100.00% (40)	<0.01 [‡]
needed therapy	87.73% (143)		72.22% (52)		100.00% (51)		100.00% (40)	<0.01 [‡]
received rehabilitation if needed	50.69% (73)		28.30% (15)		56.86% (29)		72.50% (29)	<0.01 [‡]
received therapy if needed	39.16% (56)		30.77% (16)		43.14% (22)		45.00% (18)	NS

Table 1. Characteristics of the total study cohort and the KPS-based strata

§ Subjects may endorse more than one so that percentages may not sum to 100.

Reported P values for the presence of a progressive trend across KPS strata were obtained from: *linear regression for continuous variables, [†] the χ^2 test for categorical variables and [‡] a nonparametric test of trend across ordered groups.

^f Moderated disability is defined as PF-10<35, FIM mobility subscale<30, ≥4 IADL problems.

Impairment Characteristics & Subcategories		Percent of total impairments (N)	Rehabilitation Needed	Received Rehabilitation IF Needed	Therapy Needed	Received Therapy IF Needed	Increase in Prevalence with ↓ KPS*
		100% (530)	N = 484 91.32%	N = 145 29.96%	N = 469 88.49%	N = 99 21.11%	
Subject hospitalized for impairment		12.83% (68)	100% (68)	94.12% (64)	98.53% (67)	89.71% (61)	0.001
Impairment associated with orthopedic procedure		5.09% (27)	5.58% (27)	85.19% (23)	100.00% (27)	70.37% (19)	0.02
Lymphedema	Upper Extremity	11.72% (62)	100.00% (62)	48.39% (30)	100.00% (62)	48.39% (62)	0.001 ^{\$}
	Lower Extremity	5.48% (29)	100.00% (29)	20.69% (6)	55.17% (16)	10.34% (3)	0.05
Weakness - Neurogenic	Radic/Plexop/Mononeurop	4.53% (24)	95.83% (23)	17.39% (4)	91.67% (22)	18.18% (4)	NS
Sensory Deficit - Neuropathic		3.77% (20)	95.00% (19)	21.05% (4)	95.00% (19)	5.26% (1)	NS
CTX Neuropathy	Mild	4.53% (24)	8.33% (2)	50.00% (1)	8.33% (2)	50.00% (1)	0.001 ^{\$}
	Moderate - Severe	8.87% (47)	95.74% (45)	26.67% (12)	95.74% (45)	6.67% (3)	NS
Central nervous system injury	Hemiplegia	1.51% (8)	100.00% (8)	50.00% (4)	100.00% (8)	37.50% (3)	0.014
	Myelopathy	4.53% (24)	95.83% (23)	17.39% (4)	91.67% (22)	18.18% (4)	0.01
Exertional intolerance	Deconditioning	10.19% (54)	100.00% (54)	16.67% (9)	100.00% (54)	9.26% (5)	NS
	Cardiopulmonary	9.06% (48)	100.00% (48)	10.42% (5)	100.00% (48)	6.25% (3)	NS
Joint Contracture	Hip	1.89% (10)	1.89% (10)	88.89% (8)	90.00% (9)	88.89% (8)	NS
	Shoulder	6.04% (32)	100.00% (32)	12.50% (4)	100.00% (32)	12.50% (4)	NS
	Spine	2.45% (13)	92.31% (12)	75.00% (9)	92.31% (12)	58.33% (7)	NS
Generalized motor weakness		11.70% (62)	98.39% (61)	42.62% (26)	98.39% (61)	26.23% (16)	NS
Ataxia		6.79% (36)	97.22% (35)	34.29% (12)	97.22% (35)	17.14% (6)	0.03
Myofascial dysfunction		3.40% (18)	83.33% (15)	0	83.33% (15)	0	NS
Cranial nerve dysfunction		2.21% (12)	50.00% (6)	0	50.00% (6)	0	0.018

Table 2. Impairment characteristics and subcategories: prevalences and frequencies of rehabilitation/therapy need/receipt

* P values reported for a nonparametric test of trend across ordered groups to determine if an impairment characteristic or subcategory progressively changed across KPS-based strata.

^{\$} Negative trend with decreasing impairment subcategory prevalence across KPS-based strata. All other trends were increasing.

Variables	Rehabilitation		Therapy		Variables	Rehabilitation		Therapy	
	OR	P value	OR	P value		OR	P value	OR	P value
Sociodemographic									
Age [‡]	1.04	0.76	0.98	0.864	MHI-17 [‡]	0.92	0.216	1	0.923
Caucasian	2	0.018	2.93	0.001	BPI [‡]	2.44	0.048	2.04	0.185
Marital status [§]					Function-related				
Married	1		1		KPS [‡]	0.7	<0.0001	0.87	0.199
Never married	1.38	0.344	0.94	0.902	PF-10 [‡]	0.85	0.005	0.94	0.343
Widowed	1.25	0.65	1.04	0.946	OARS ADL [§]				
Divorced	1.21	0.622	0.33	0.013	6-7 ADL problems	1		1	
Separated	0.88	0.766	0.57	0.156	4-5 ADL problems	1	0.987	0.58	0.339
Live					1-3 ADL problems	0.85	0.691	0.67	0.406
alone	0.75	0.401	0.63	0.273	No ADL problems	0.42	0.038	0.49	0.123
with husband	1.47	0.157	0.89	0.719	OARS IADL[§]				
with children	1.89	0.022	1.58	0.142	6-7 IADL problems	1		1	
with grandchildren	0.6	0.343	0.61	0.425	4-5 IADL problems	0.71	0.294	0.98	0.952
with parents	0.47	0.053	0.49	0.158	1-3 IADL problems	0.46	0.028	0.77	0.502
with siblings	0.85	0.775	0.8	0.776	No IADL problems	0.55	0.299	1.03	0.965
with friends	0.6	0.25	3.37	0.107	FIM mobility*				
with paid helper	0.22	0.001	0.25	0.097	Less than full strength	1.37	0.233	0.91	0.751
Vocation:					Impairment specific				
Employed full time	0.58	0.196	0.75	0.586	Hospitalization	66.17	<0.0001 [†]	97.39	<0.0001 [†]
Employed part time	0.33	0.111	0.32	0.249	Orthopedic procedure	15.79	<0.0001	10.75	0.001
Retired - no disability	1.2	0.521	0.85	0.619	Weakness - neurogenic	0.48	0.175	0.82	0.719
Retired - disability	1.6	0.115	1.58	0.18	Lymphedema UE	2.32	0.004	4.59	<0.0001
Unemployed - seeking	0.21	0.101	0.33	0.235	Lymphedema LE	0.59	0.268	0.86	0.808
Unemployed - not					Hemiplegia	2.38	0.216	1.25	0.788
seeking	1	0.991	1.19	0.668	Myelopathy	3.9	0.014	1.69	0.37
Student	1.41	0.61	2.28	0.227	Cranial nerve dysfunction	0.02	<0.001	0.01	<0.001
Source of income					CTX neuropathy: mild	2.35	0.543	3.77	0.343
Employment	0.85	0.606	1	0.999	CTX neuropathy: mod-				
Rentals, investments	1.76	0.048	1.72	0.102	severe	0.84	0.599	0.24	0.015
Social security	0.66	0.204	0.55	0.093	Generalized musc				
Disability payments	0.98	0.959	1.03	0.94	weakness	1.9	0.021	1.39	0.259
Unemployment comp.	0.89	0.391	0.37	0.319	Shoulder				
Retirement pension	1.43	0.266	1.53	0.229	contracture/tendon.	0.32	0.033	0.51	0.219
Aid from family	0.49	0.341	0.8	0.772	Hip contracture	19.74	0.005	32.44	0.001
Aid from organizations	3.58	<0.0001	5.75	<0.0001	Spine contracture/instabil.	7.41	0.003	5.55	0.005
Cancer-specific									
Duration of Stage IV disease	1	0.094	1	0.088	Ataxia	1.24	0.595	0.76	0.586
Number of CTX regimens	1.02	0.785	0.92	0.235	Exert. Intol: deconditioning	0.43	0.018	0.35	0.018
Number of metastatic sites	0.98	0.879	0.86	0.251	Exert. Intol:				
Number XRT treatments	1.61	0.087	1.03	0.802	cardiopulmonary	0.25	0.003	0.23	0.013
History of ca.-related surgery	1.39	0.021	1.66	0.001	Myofascial dysfunction	0.04	<0.001	0.01	<0.001
Bone metastases	2.72	0.001	1.58	0.156	Sensory deficit:				
Brain metastases	0.8	0.545	0.59	0.21	neuropathic	0.61	0.37	0.2	0.112
Lung metastases	0.91	0.725	1.03	0.923					
Liver metastases	1.3	0.368	0.97	0.915					

Table 3. Bivariable analyses of subject and impairment characteristics and receipt of rehabilitation or therapy

[§] Categorical and ordinal variables included in logistic regressions as dummy variables.

* The OR listed reflects the likelihood of receiving rehabilitation with a 5 point increase in FIM mobility subscale score.

[†]Covariate associated with the highest log likelihood among all univariate logistic regressions

[†] The OR listed reflects the likelihood of receiving rehabilitation/therapy with a 10 point change in age; as well as PF-10, MHI-17, KPS, and BPI scores.

Characteristic	Adjusted Odds Ratio	Robust Standard Error [§]	P value	95% Confidence Interval	
Impairment required hospitalization*	87.88	50.55	<0.0001	28.46	271.36
Impairment associated with an orthopedic procedure*	10.12	4.08	<0.0001	4.59	22.30
Impairment = arm lymphedema*	7.21	2.55	<0.0001	3.61	14.43
Caucasian ethnicity†	2.99	1.16	0.01	1.40	6.42
Subject receiving unemployment benefits†	0.21	1.70	<0.0001	0.10	0.41
Subject unemployed and looking for work†	0.05	0.02	<0.0001	0.02	0.13

Table 4. Multiple logistic regression analyses of subject and impairment characteristics associated with receipt of rehabilitation

§ Robust standard error is adjusted for clustering by subject

* Impairment-level covariate

† Subject-level covariate

Characteristic	Adjusted Odds Ratio	Robust Standard Error [§]	P value	95% Confidence Interval	
Impairment required hospitalization*	558.75	312.06	0	186.99	1669.61
Impairment = arm lymphedema*	69.59	32.93	0	27.53	175.93
Caucasian Ethnicity†	5.68	2.78	0	2.18	14.82
Subject retired on disability†	2.84	1.46	0.04	1.04	7.77

Table 5. Multiple logistic regression analyses of subject and impairment characteristics associated with receipt of therapy

§ Robust standard error is adjusted for clustering by subject

* Impairment-level covariate

† Subject-level covariate

Supporting Data

eINTEGRA SPECT scans from 2 study subjects

